

What is claimed is:

1. An isolated DNA comprising one or more consensus or near consensus splice sites which have been corrected to increase expression of the DNA.
2. The isolated DNA of claim 1 comprising a cDNA clone.
3. The isolated DNA of claim 1, wherein the one or more consensus or near consensus splice sites are corrected by conservative mutation of at least one consensus nucleotide.
4. The isolated DNA of claim 3, wherein the maximum number of conservative mutations are made within the one or more consensus or near consensus splice sites.
5. The isolated DNA of claim 1 wherein the one or more consensus or near consensus splice sites comprises a 5' splice donor site which is corrected by mutating one or both of the nucleotides within the essential GT pair.
6. The isolated DNA of claim 1 wherein the one or more consensus or near consensus splice sites comprises a 3' splice acceptor site which is corrected by mutating one or both of the nucleotides within the essential AG pair.
7. The isolated DNA of claim 1 comprising a nucleotide sequence which encodes a Factor VIII protein.
8. The isolated DNA of claim 1 comprising a cDNA which is expressed as a  $\beta$ -domain deleted Factor VIII protein.
9. The isolated DNA of claim 8 comprising the nucleotide sequence shown in SEQ ID NO:1.
10. The isolated DNA of claim 1 comprising the coding region of a full-length Factor VIII gene, wherein the coding region contains an intron spanning all or a portion of the gene encoding the  $\beta$ -domain.
11. The isolated DNA of claim 8 further comprising a second intron upstream of the coding region.

12 An isolated DNA comprising the coding region of a full-length Factor VIII gene, wherein the coding region contains an intron spanning the portion of the gene encoding the  $\beta$ -domain.

13 The isolated DNA of claim 12 comprising the coding region of the nucleotide sequence shown in SEQ ID NO:3.

14. The isolated DNA of claim 12 further comprising one or more consensus or near consensus splice sites which have been corrected.

15. An isolated DNA which is expressed as a  $\beta$ -domain deleted Factor VIII protein, said DNA comprising the coding region of a full-length Factor VIII gene modified to (a) correct one or more consensus or near consensus splice sites within the coding region and (b) to incorporate an intron into the coding region which spans the portion of the gene encoding the  $\beta$ -domain.

16. The isolated DNA of claim 15 which encodes a human  $\beta$ -domain deleted Factor VIII protein.

17. An expression vector comprising the isolated DNA of claim 1 operably linked to a promoter sequence.

18. An expression vector comprising the isolated DNA of claim 7 operably linked to a promoter sequence.

19. An expression vector comprising the isolated DNA of claim 10 operably linked to a promoter sequence.

20. An expression vector comprising the isolated DNA of claim 12 operably linked to a promoter sequence.

21. A molecular complex comprising the expression vector of claim 17 linked to an agent which binds to a component on the surface of a mammalian cell.

22. A molecular complex comprising the expression vector of claim 18 linked to an agent which binds to a component on the surface of a mammalian cell.

23. A molecular complex comprising the expression vector of claim 19 linked to an agent which binds to a component on the surface of a mammalian cell.

5 24. A molecular complex comprising the expression vector of claim 20 linked to an agent which binds to a component on the surface of a mammalian cell.

25. A method of increasing expression of a gene comprising correcting one or more consensus or near consensus splice sites within the nucleotide sequence of the gene.

10 26. The method of claim 25 wherein the step of correcting the one or more consensus or near consensus splice sites comprises conservatively mutating one or more consensus nucleotides within the consensus or near consensus splice site.

15 27. The method of claim 25 wherein the step of correcting the one or more consensus or near consensus splice sites comprises making the maximum number of conservative mutations possible to consensus nucleotides within the consensus or near consensus splice site.

20 28. The method of claim 25 comprising mutating one or both of the nucleotides within the essential GT pair, if the consensus or near consensus splice site is a 5' splice site, or mutating one or both of the nucleotides within the essential AG pair, if the consensus or near consensus splice site is a 3' splice site.

25 29. The method of claim 28 wherein the gene encodes a Factor VIII protein.

30 30. The method of claim 25 wherein the gene is expressed as a  $\beta$ -domain deleted Factor VIII protein.

35 31. The method of claim 30 wherein the gene comprises the nucleotide sequence shown in SEQ ID NO:1.

32. The method of claim 25 wherein the gene comprises the coding region of a full-length Factor VIII gene, and the method further comprises the step of inserting an intron into the coding region of the gene so that the intron spans all or a portion of the segment of the gene encoding the  $\beta$ -domain.

33. The method of claim 32 further comprising inserting a second intron upstream of the coding region of the gene.

34. A method of increasing expression of a gene encoding Factor VIII comprising inserting into the coding region of the gene an intron which spans all or a portion of the portion of the gene encoding the  $\beta$ -domain.

35. The method of claim 34 further comprising correcting one or more consensus or near consensus splice sites within the Factor VIII gene by conservative mutation of a consensus nucleotide.

36. A method of increasing expression of a gene encoding Factor VIII comprising correcting one or more consensus or near consensus splice sites within the gene.

37. The method of claim 36 wherein the correction is made by conservative mutation of a consensus nucleotide located within the coding region of the gene.

38. A method of producing Factor VIII comprising introducing the expression vector of claim 19 into a host cell capable of expressing the vector, and allowing for expression of the vector.

39. A method of producing Factor VIII comprising introducing the expression vector of claim 20 into a host cell capable of expressing the vector, and allowing for expression of the vector.

40. An expression vector comprising a liver-specific promoter and a liver-specific enhancer, said promoter and enhancer being derived from different genes.

41. The expression vector of claim 40, wherein the promoter and enhancer are located upstream from the coding sequence of a gene.

42. The expression vector of claim 41, wherein the coding sequence is expressed as a  $\beta$ -domain deleted human Factor VIII protein.

43. The expression vector of claim 40, wherein the liver-specific promoter is the human thyroid binding globulin promoter.

44. The expression vector of claim 40, wherein the liver-specific enhancer is the alpha-1 microglobulin/bikunin enhancer.

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45. The expression vector of claim 41 further comprising one or more introns located (a) downstream from the promoter and enhancer and (b) upstream from the coding sequence.

5 46. The expression vector of claim 45, wherein the intron is located within the leader sequence of the gene.

47. The expression vector of claim 45, wherein the intron comprises one or more consensus splice sites.

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48. The expression vector of claim 46, wherein the leader sequence has no secondary structure when transcribed as RNA.

15 49. The expression vector of claim 41, wherein the 3' untranslated region of the gene is modified to increase processing, export or stability of the mRNA transcribed from the gene.

20 50. An expression vector comprising the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer.

51. The expression vector of claim 50 comprising two or more copies of the alpha-1 microglobulin/bikunin enhancer.

25 52. The expression vector of claim 50, wherein the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer are located upstream from the coding sequence of a gene.

30 53. The expression vector of claim 52, wherein the coding sequence is also preceded upstream by a leader sequence comprising one or more introns.

54. The expression vector of claim 51 wherein the coding sequence is expressed as a  $\beta$ -domain deleted human Factor VIII protein.

35 55. The expression vector of claim 53, wherein the intron comprises a consensus 5' splice donor site, and a consensus 3' splice acceptor site.

56. The expression vector of claim 53, wherein the intron has no secondary structure when transcribed as RNA.

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